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<u>REMARKS</u>

Status of the Claims

Claims 32 and 35 has been amended to recite <u>intradermally or subcutaneously</u> administering (or delivering) total tumor cell RNA to <u>cutaneous</u> cells. Support for this amendment can be found, for example, on page 5, lines 19-26, and in Examples 2 and 3 (pages 26 and 27) of the application. Claim 35 also now recites, wherein the total tumor cell RNA is taken from an <u>autologous</u> tumor associated with the cancer. Claims 37-42 have been canceled without prejudice or disclaimer. Claim 43 has been amended to recite administering <u>RNA which comprises</u> antigen RNA, and to specify that the antigen is an allogenic transplant tissue antigen. Claims 50-53 have been added. Support for these claims can be found, for example, on page 21, lines 22-25 of the application.

Claims 32-36 and 43-46 and 50-53 are pending and at issue.

Claim Objections

The Examiner has objected to claims 44 and 45 as being in improper dependent form. The Examiner alleges that claims 44 and 45, which respectively recite cellular RNA and cellular mRNA, are broader than claim 43, which previously recited antigen RNA. Claim 43 has been amended to recite "RNA which comprises antigen RNA". Applicant respectfully submits that claims 44 and 45 are in proper dependent form.

Claim Rejections - 35 U.S.C. § 112, first paragraph

Claims 32-36 stand rejected as not enabled by the specification. The Examiner admits that the specification is enabling for inducing an immune response to a tumor in a subject by

¹ Applicant respectfully submits, however, that claims 37-42 are patentable, and reserves the right to prosecute these claims in a continuation application.

² Applicant also respectfully submits that claim 43 is patentable when the antigen is an autoantigen, or allergen, and reserves the right to prosecute claims directed to this subject matter in a continuation application.

intradermal or subcutaneous administration of total tumor cell RNA, wherein the tumor cells are autologous or taken from the same type of allogenic tumor. To advance prosecution, claim 32 has been amended to recite a method which comprises intradermally or subcutaneously administering total tumor cell RNA... Claim 32 previously recited "wherein the total tumor cell RNA is from tumor cells from the subject." Claim 35 has been amended to recite intradermally or subcutaneously delivering... total tumor cell RNA to cutaneous cells... wherein the total tumor cell RNA is taken from an autologous tumor associated with the cancer. Applicant respectfully requests that the enablement rejection be withdrawn.

Claims 43-49 stand rejected as not enabled by the specification. The Examiner admits that the specification is enabling for inducing tolerance to an allogenic transplant antigen in a subject by intravenously administering total cellular RNA or total cellular mRNA at least seven days prior to the allogenic transplantation, wherein the cells are from the graft tissue or spleen.

Claim 43 has been amended to specify that the antigen is an allogenic transplant tissue antigen.³

Applicant respectfully disagrees with the Examiner's requirement that the claims be limited to RNA from graft tissue or spleen. Although the Examiner is correct in noting that "specificity is a hallmark of acquired immunity/tolerance", such specificity is instantly provided by RNA which includes antigen RNA, as recited in claim 43. A person of ordinary skill in the art would be able to select appropriate cell types --such as splenic cells or graft tissue cells -- which include antigen RNA. The claims should not be limited only to those cell types explicitly shown to contain antigen RNA, as the criteria for selecting donor RNA cells is clearly set forth. "[A] considerable amount of experimentation is permissible . . . if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should

³ Applicant respectfully disagrees with the Examiner's assertion (beginning on page 8 of the Office Action) that Applicant has not disputed the underlying basis for the Examiner's opinion that induction of tolerance to autoantigens and allergens is not enabled. In view of the amendments made herein, however, this argumentation is moot. Applicant reserves the right to revisit these contentions in a continuation application.

proceed". *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Other suitable cells which contain antigen RNA will present themselves to a person of ordinary skill.

Applicant also respectfully disagrees with the Examiners' requirement that the claims specify the timing of the RNA administration. The timing of the antigen RNA administration is not an inventive aspect of the present invention, and the Examiner admits that the proper timing to trigger an immune response is "well known in the art". The courts explain:

Claims are not rejected as broader than the enabling disclosure under 35 U.S.C. § 112 for noninclusion of limitations dealing with factors which must be presumed to be within the level of ordinary skill in the art; the claims need not recite such factors where one of ordinary skill in the art to whom the specification and claims are directed would consider them obvious.

In re Skrivan, 427 F.2d 801, 806 (CCPA 1970). To the contrary, not everything necessary to practice the invention needs to be disclosed--much less recited in the claims. What is well known is best omitted. MPEP § 2164.08, citing *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991).

Applicant respectfully requests that the rejection of claims 43-49 under 35 U.S.C. § 112 be withdrawn.

Claim Rejections - 35 U.S.C. § 103

Claim 32 stands rejected as obvious over Qiu (Gene Ther 1996;3:262-68) in view of Nair (U.S. Pat. No. 5,853,719). Claim 33 stands rejected over Qui, in view of Nair, and further in view of Segal (U.S. Patent No. 6,403,080).

Qiu teaches that the use of a gene gun to introduce mRNA from human alpha 1 antitrypsin results in a positive antibody response. Qiu does not teach use of total tumor cell RNA, or that an immune response against a tumor can be created thereby. Nair teaches that a RNA-enriched tumor preparation can be used in lieu of purified RNA preparation for pulsing a purified population of blood or lymphoid derived dendritic cells.

There is no motivation to combine Qiu and Nair, and even if combined, there is no reasonable expectation of success. The primary reference, Qiu, does not disclose or suggest administration of fractionated tumor cell RNA or total tumor cell RNA. There is no motivation to consult Nair, which suggest the interchangibility of the two, when the use of tumor cell RNA is not taught or suggested in Qiu.

Nevertheless the Examiner concludes, presumably based on the teaching of the present application, that it would have been obvious to substitute the antigens in Qui with total tumor cell RNA. Even if this were the case, there is no reasonable expectation of success upon making this purportedly obvious substitution. Qui and Nair disclose different routes of administration, i.e., Qui discloses particle bombardment of the epidermis and liver, whereas Nair exclusively teaches intraperitoneal vaccination or vaccination via infusion. In Nair, a purified population of blood or lymphoid derived dendritic cells were pulsed *ex vivo*, as opposed to an *in vivo* heterogenous population of epidermal cells. Neither reference discloses or suggests that an immune response to a tumor can be induced by intradermally or subcutaneously administering total tumor cell RNA to epidermal cells.

Segal seeks to provide compositions and methods for improved vaccines by improving the uptake of antigens by antigen presenting cells upon introduction of opsonin-enhanced cells which comprises the selected antigen. Fibrosarcoma cells are one of the antigens mentioned in Segal. Segal does not, however, disclose or suggest that an immune response to a tumor can be induced by intradermally or subcutaneously administering total tumor cell RNA to epidermal cells, or provide motivation to combine Qui and Nair.

Applicant respectfully requests that the obviousness rejection of claims 32 and 33 be withdrawn.

Claims 37-42 have been rejected as obvious over Ashley (J. Exp. Med. 186:1177-82) in view of Beissert (J. Immunol. 154:1280-86). These claims have been canceled without prejudice, rendering this rejection moot.

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In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

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Respectfully submitted,

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